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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NICHOLS, CHRISTOPHER J	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 03/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/620,955	HUSTON ET AL.	
	Examiner	Art Unit	
	Christopher J Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-93* is/are pending in the application.

4a) Of the above claim(s) *6 and 24-93* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 7-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-93* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 July 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group 1 (claims 1-5 and 7-23), huntingtin, and intrabody in the response filed 10 September 2003 is acknowledged.

Drawings

2. The drawings are objected to because Figures 3-8 and 12-15 are too dark to decipher the information contained therein. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

3. The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference sign(s) not mentioned in the description: the last panel in Figure 8 "8H". A proposed drawing correction, corrected drawings, or amendment to the specification to add the reference sign(s) in the description, are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Claim Objections

4. Claims **2** and **7** are objected to because of the following informalities: said claims recite non-elected subject matter. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims **1-5** and **7-23** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *an in vitro method for inhibiting the formation of huntingtin aggregates comprising the step of contacting said huntingtin with an intrabody comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 4, and SEQ ID NO: 6*, does not reasonably provide enablement for *practicing said method in vivo, on any other aggregating polypeptide, or using any other agent.* The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to **make** or **use** the invention commensurate in scope with these claims.

6. The claims are drawn very broadly to a method of inhibiting the formation of intracellular aggregates comprising administering a polypeptide-binding molecule which reduces said aggregation. The language of said claims encompasses both *in vivo* and *in vitro* use, at least 15 clinically diverse amyloid aggregate related diseases and disorders, and at least 8 CAG repeat disorders {see Sipe "Amyloidosis" Ann. Rev. Biochem. **61**: 947-975 and Tobin & Signer (December 2000) "Huntington's disease: the challenge for cell biologists." Trends Cell Biol. **10**(12): 531-536}. The breadth of the claim also encompasses aggregate related diseases and disorders which have yet to be characterized.

7. The above invention is drawn to a method of reducing or completely inhibiting the formation of intracellular aggregates comprising contacting cells or a patient samples with an intrabody that binds to an aggregating polypeptide and therein reduce aggregation.

8. The specification teaches that an anti-huntingtin intrabody, α-Nt-HD-C4-sFv can be used to reduce aggregate formation and cell toxicity in an *in vitro* cell model (Figures 14 & 15).

9. The specification fails to provide any guidance for the successful treatment of any aggregate related disease, disorder, or condition. And since the resolution of the various complications with regard to the role of polypeptide aggregation in disease is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations with known pathological related proteins, signs, and symptoms to correlate with relief due to administration of the as of yet identified "polypeptide-binding molecule". In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

10. Additionally, a person skilled in the art would recognize that predicting the efficacy of using a single example of a polypeptide-binding molecule, α-Nt-HD-C4 sFv *in vivo* based solely on its performance *in vitro* is highly problematic (see MPEP §2164.02). Thus, although the specification prophetically considers and discloses general methodologies of using the claimed methods in *in vivo*, such a disclosure would not be considered enabling since the state of aggregate related diseases, disorders, and conditions is highly unpredictable. The factors listed

below have been considered in the analysis of enablement [see MPEP §2164.01(a) and *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)]:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

11. The following references are cited herein to illustrate the state of the art of aggregate related diseases, conditions, and disorders.

12. On the nature of the invention, polypeptide aggregates are often complex cellular structures known as "aggresomes". Waelter *et al.* (May 2001) "Accumulation of Mutant Huntington Fragments in Aggresome-like Inclusion Bodies as a Result of Insufficient Protein Degradation." Molecular Biology of the Cell **12**(5): 1393-1407 teaches that huntingtin exon 1 proteins with polyglutamine stretches of 51 to 83 repeats formed aggresome-like inclusions (2,3, & 5). Further Kopito (December 2000) "Aggresomes, inclusion bodies and protein aggregation." Trends in Cell Biology **10**(12): 524-530 teaches that although protein aggregates are often related to pathology such as in Huntington's disease, not all aggregates are pathological *per se* (pp. 524). Kopito teaches that aggresomes are deliberately assembled subcellular structures where cells sequester or "quarantine" foreign or misfolded protein (Figure 1; pp. 528-529). Thus the formation of the aggregate itself may be a "self-defense mechanism" by the cell. In addition, Johnston *et al.* (28 December 1998) "Aggresomes: A Cellular Response to Misfolded Proteins." The Journal of Cell Biology **143**(7): 1883-1898 teaches that aggresomes are

formed via active transport of their components along microtubules to congregate at the MTOC (Microtubule Organizing Center) (Figures 1, 4, & 8). Thus the aggregates which are the target of the claims are not all passive clumps of protein but are formed in active cell-based responses, increasing the complexity and unpredictability of responses to any given "polypeptide-binding molecule". Therefore insufficient guidance is present in the Specification to support the full scope of the claims to any aggregating polypeptide as only huntingtin has been fully disclosed.

13. On the state of the prior art, Leavitt *et al.* (1999) "Recent Insights into Molecular Pathogenesis of Huntington Disease." Seminars in Neurology **19**(4): 385-395 teaches that while aggregates are a cardinal sign of Huntington's disease (HD) their role in pathology is unclear. Leavitt *et al.* teaches that improper protein processing by enzymes such as caspases (enzymes involved in triggering apoptosis pathways) may yield "toxic fragments" which are the culprits in causing HD not the aggregates themselves (Figure 2). This is supported by the observation that neurological abnormalities observed in mice expressing exon 1 of huntingtin with an expanded glutamine tract are delayed when crossed with mice expressing a modified caspase–1 that inhibits endogenous caspase–1 (a dominant negative caspase) or when treated with the broad-spectrum caspase inhibitor V-VAD-FMK (pp. 194).

14. This is further supported by Kim *et al.* "Mutant Huntingtin Expression in Clonal Striatal Cells: Dissociation of Inclusion Formation and Neuronal Survival by Caspase Inhibition." The Journal of Neuroscience **19**(3): 964-973 who found that treatment with protease inhibitors, Z-VAD-FMK and Z-IETD-FMK reduced the portion of neurons that formed aggregates but this was not associated with increased survival. Kim *et al.* suggest that aggregate formation may not be sufficient and necessary to trigger cell death and thus prevention or reduction thereof may not

have any effect (Figure 7; pp. 972). Therefore a "polypeptide-binding molecule" which decreases aggregate may not be effective as a therapeutic agent.

15. On the level of predictability, Wigley *et al.* (3 May 1999) "Dynamic Association of Proteasomal Machinery with the Centrosome." The Journal of Cell Biology **145**(3): 481-490 teaches that aggresomes contain 26S proteasomes, HSP70, HSP90, and ubiquitin and are formed in response to mutated or misfolded proteins (Figures 1, 6, & 7). Also García-Mata *et al.* (20 September 1999) "Characterization and Dynamics of Aggresome Formation by Cytosolic GFP-Chimera." The Journal of Cell Biology **146**(6): 1239-1254 teaches that a N-terminal GFP chimera of p115 formed an aggresome but not the C-terminal GFP chimera of p115 (Figure 2). Thus the formation of aggresomes, the active cell-based aggregates, may vary on their conformation. Further Waelter *et al.* (May 2001) "Accumulation of Mutant Huntington Fragments in Aggresome-like Inclusion Bodies as a Result of Insufficient Protein Degradation." Molecular Biology of the Cell **12**(5): 1393-1407 teaches that the aggresomes formed by huntingtin are also active and respond to proteasome inhibition (Figure 4). As noted above, different arrangements of the same components in a fusion protein will yield different results, one can not readily predict the response of a cell to a given aggregating or non-aggregating polypeptide. Therefore insufficient guidance is present in the Specification to support the full scope of the claims as only huntingtin has been disclosed.

16. More over on the nature of the invention, Chen *et al.* (May 1994) "Intracellular Antibodies as a New Class of Therapeutic Molecules for Gene Therapy." Human Gene Therapy **5**(5): 595-601 teaches that intracellularly expressed antibodies, "intrabodies" are a form of gene therapy which are designed to be delivered via an encoding nucleic acid, expressed in the target

cell, then bind and inactivate the target polypeptide inside the cells (pp. 595). It is noted that the claims as currently presented read on any "polypeptide-binding molecule" but the elected embodiment of the claims is an "intrabody". Thusly as a form of gene therapy, several critical factors must be adequately addressed to allow for the full enablement of the invention.

17. The first critical factor to be addressed is the delivery vehicle (also known as a "vector" in the art) as addressed by Kaneda (September 2001) "Gene Therapy: A Battle Against Biological Barriers." Current Molecular Medicine **1**(4): 493-499. Kaneda teaches that gene therapy to be successful must accomplish four key goals: (1) Vectors must reach target cells (pp. 495), (2) Vector must introduce the therapeutic nucleic acid into target cell (pp. 495), (3) The therapeutic nucleic acid must translocate into the nucleus of the target cell (pp. 495-496), and (4) The therapeutic nucleic acid must achieve stable retention and expression (pp. 496-497). In Huntington's disease (but one of the aggregate related disorders in the claims as currently presented) the first signs of cytotoxicity are in medium spiny GABAergic neurons in the striatum. This cell death is then followed by a dorsal "wave of pathology" through the patient's brain but most damaging to the striatum. In contrast, the neighboring large cholinergic neurons of the striatum are largely unaffected in HD. Therefore the skilled artisan must find a way to target the claimed therapeutic polypeptide-binding molecule, whether a therapeutic nucleic acid or not, into these medium spiny GABAergic neurons but not into the unaffected cholinergic neurons of the striatum. The skilled artisan must find a way to overcome the innate immune defenses that confound gene therapy, as well as crossing the blood brain barrier (BBB), making its way through brain tissue to reach the medium spiny GABAergic neurons deep in the striatum.

18. Moreover Verma & Somia (18 September 1997) "Gene Therapy—promises, problems and prospects." Nature **389**: 239-242 teach that even if the therapeutic vector reaches the target cell it still must overcome innate cellular defenses such as RNAase. In addition, the therapeutic vector must successfully be expressed; the protein folded, and then reach its target (Figure 1). Pfeifer & Verma (2001) "Gene Therapy: Promises and Problems." Annu. Rev. Genomics Hum. Genet. **2**:177-211 teach that potential therapeutic vectors are a large and diverse group each with its own advantages and disadvantages. The claims thus present an invitation to experiment, first to identify the disease to be targeted, then the vector to be used, and then the therapeutic administration of said therapeutic vector (pp. 178-180). The Specification as filed provides insufficient guidance on how to make such a therapeutic vector and how to use said therapeutic vector.

19. On the nature of the invention in regards to the target and the intrabody, the skilled artisan readily recognizes that protein chemistry is an unpredictable area of biotechnology. Proteins with deletion, insertion or substitution/replacement of single amino acid residues may lead to both structural and functional changes in biological activity and immunological recognition, see in particular Skolnick & Fetrow (2000) "From genes to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39. For example, Jobling & Holmes (1991) "Analysis of structure and function of the B Subunit of cholera toxin by the use of site-directed mutagenesis." Molecular Microbiology **5**(7): 1755-67 teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis which produce proteins that differ in native conformation, immunological recognition, binding and toxicity. The skilled artisan further recognizes that immunological

responses may depend upon the structural characteristics (conformation) of the particular protein (amino acid sequence) targeted. Thus, both biological function and immunological recognition are unpredictable properties which must be experimentally determined. Further it is noted, that for particularly small peptides, conjugation appears to be required for promoting an effective immune response. Since the specification as filed does not specify sufficiently the epitopes or vectors to be used for the full range of the claims, it constitutes an invitation to experiment in the absence of guidance.

20. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *in vitro* experiments to the *in vivo* inhibition of polypeptide aggregates as exemplified in the references herein.

21. Claims **1-5, 7-9, 11-20,** and **23** are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

22. The claims require a "polypeptide-binding molecule" which minimizes aggregation while not providing any particular conserved structure, or other distinguishing feature, such as a specific biological activity thus implying that the activity of the agent used is not known or must be confirmed. Further regarding the molecule, the art recognizes that "molecule" can pertain to chemical entities, pharmaceutical compositions, proteins, peptides, non-peptide compounds, animal tissue extracts, nucleic acids, antisense molecules, peptidomimetic, transformed cells,

radiation, antibodies, antibody fragments, cyclic peptides, agonists, antagonists, inhibitors, enhancers, vegetable extracts, cell extracts, synthetic agents, biologically derived substances as well as proteinaceous substances, known, and unknown compounds. Thus, the claims are drawn to a genus of agents that is defined only by a desired activity.

23. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, and any combination thereof. In this case, the only factor present in the claim that is sufficiently disclosed is in the form of a recitation of a desired activity. The specification does not identify any particular portion of the structure that must be conserved, nor does it provide a disclosure of structure/function correlation. The distinguishing characteristics of the claimed genus are not described. Accordingly, the specification does not provide adequate written description of the claimed genus.

24. To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. *Vas-Cath*, 935 F.3d at 1563; see also *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 [41 USPQ2d 1961] (Fed. Cir. 1997) (patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention"); *In re Gosteli*, 872 F.2d 1008, 1012 [10 USPQ2d 1614] (Fed. Cir. 1989) ("the description must clearly allow persons of ordinary skill in the art to recognize that [the inventor]

invented what is claimed"). Thus, an applicant complies with the written-description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572.

25. See *University of Rochester v. G.D. Searle & Co.*, 68 USPQ2d 1424 (DC WNY 2003) and *University of Rochester v. G.D. Searle & Co. et al.* CAFC [(03-1304) 13 February 2004]. In *University of Rochester v. G.D. Searle & Co.* a patent directed to method for inhibiting prostaglandin synthesis in human host using an unspecified compound, in order to relieve pain without side effect of stomach irritation, did not satisfy written description requirement of 35 U.S.C. §112, since the patent described the compound's desired function of reducing activity of the enzyme PGHS-2 without adversely affecting PGHS-1 enzyme activity, but did not identify said compound, since invention consists of performing "assays" to screen compounds in order to discover those with desired effect. The patent did not name even one compound that assays would identify as suitable for practice of invention, or provide information such that one skilled in art could identify suitable compound. And since specification did not indicate that compounds are available in public depository, the claimed treatment method cannot be practiced without compound. Thus the inventors cannot be said to have "possessed" claimed invention without knowing of a compound or method certain to produce compound. Thus said patent constituted an invitation to experiment to first identify, then characterize, and then use a therapeutic a class of compound defined only by their desired properties.

26. In addition, the claims require an intrabody which binds to a "polypeptide capable of forming said aggregates" while the claims do not specify an epitope, a specific peptide, nor do

the claims require that the antibody's target possess any particular conserved structure, such as a domain or motif, or other distinguishing feature, such as a sequence. Thus, the claims are drawn to a genus of intrabodies that is defined by binding anywhere, anyhow to any given polypeptide which is capable of forming intracellular aggregates.

27. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical, structure/function correlation, methods of making the claimed product, and any combination thereof. In this case, the only factor present in the claim that is sufficiently disclosed is a recitation of a massive genus of desired targets for the intrabody in question. The specification does not identify any particular portion of the targets that must be conserved, nor does it provide an epitope. The distinguishing characteristics of the claimed genus are not described. Accordingly, the specification does not provide adequate written description of the claimed genus.

28. In *Randolph J. Noelle v Seth Lederman, Leonard Chess and Michael J. Yellin* (CAFC, 02-1187, 20 January 2004) the CAFC held that "Therefore, based on our past precedent, as long as an applicant has disclosed a "fully characterized antigen," either by its structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository, the applicant can then claim an antibody by its binding affinity to that described antigen.

29. Noelle did not provide sufficient support for the claims to the human CD40CR antibody in his '480 application because Noelle failed to disclose the structural elements of human CD40CR antibody or antigen in his earlier '799 application. Noelle argues that because

antibodies are defined by their binding affinity to antigens, not their physical structure, he sufficiently described human CD40CR antibody by stating that it binds to human CD40CR antigen. Noelle cites Enzo Biochem II for this proposition. This argument fails, however, because Noelle did not sufficiently describe the human CD40CR antigen at the time of the filing of the '799 patent application. In fact, Noelle only described the mouse antigen when he claimed the mouse, human, and genus forms of CD40CR antibodies by citing to the ATCC number of the hybridoma secreting the mouse CD40CR antibody. If Noelle had sufficiently described the human form of CD40CR antigen, he could have claimed its antibody by simply stating its binding affinity for the "fully characterized" antigen. Noelle did not describe human CD40CR antigen. Therefore, Noelle attempted to define an unknown by its binding affinity to another unknown. As a result, Noelle's claims to human forms of CD40CR antibody found in his '480 application cannot gain the benefit of the earlier filing date of his '799 patent application.

30. Moreover, Noelle cannot claim the genus form of CD40CR antibody by simply describing mouse CD40CR antigen."

31. Therefore the full breadth of the claim fails to meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision.

32. Claims **1, 10,** and **11** are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "specifically" in claim 1 is a relative term which renders the claim indefinite. The term "specifically" is not defined by the claim, the specification

does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The claims have not specified an epitope nor a particular structure to which the intrabody binds thus it is not clear what is meant by "specifically".

Summary

33. No Claims are allowed.

34. The Examiner notes that polyglutamine disorders are also known as "CAG repeat diseases" and intracellular aggregates may also be referred to as "inclusions" in the art.

35. The following published US patent applications were found by the Examiner during the art search. Although these applications have a later filing date than the instant application and are not used for the basis of a rejection, they may be of interest to Applicant:

a. US 2002/0160952 A1 (31 October 2002) Kazantsev *et al.*

b. US 2003/0229019 A1 (11 December 2003) Burke *et al.*

c. US 2003/0232052 A1 (18 December 2003) Khoshnan *et al.*

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is **(571) 272-0889**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on **(571) 272-0887**.

The fax number for the organization where this application or proceeding is assigned is **703-872-9306**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see **http://pair-direct.uspto.gov**. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

CJN
March 24, 2004

Gary L. Kunz

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